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=> d l7 1-11 bib ab

L7   ANSWER 1 OF 11     MEDLINE on STN                  DUPLICATE 1
AN   2008014164     MEDLINE
DN   PubMed ID: 17942753
TI   Multiple signaling pathways promote B lymphocyte stimulator dependent
     B-cell growth and survival.
AU   Woodland Robert T; Fox Casey J; Schmidt Madelyn R; Hammerman Peter S;
     Opferman Joseph T; Korsmeyer Stanley J; Hilbert David M; Thompson Craig B
CS   Department of Molecular Genetics and Microbiology, University of
     Massachusetts Medical School, Worcester 01655, USA..
     Robert.Woodland@umassmed.edu
NC   AI041054 (United States NIAID)
     AI057463 (United States NIAID)
     DK32520 (United States NIDDK)
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SO Blood, (2008 Jan 15) Vol. 111, No. 2, pp. 750-60. Electronic Publication: 2007-10-17.
Journal code: 7603509. ISSN: 0006-4971.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200803
ED Entered STN: 10 Jan 2008
Last Updated on STN: 12 Mar 2008
Entered Medline: 11 Mar 2008
AB We investigated the mechanism by which B lymphocyte stimulator (BLyS)/BAFF, a tumor necrosis factor superfamily ligand, promotes B-cell survival and resistance to atrophy. BLyS stimulation activates 2 independent signaling pathways, Akt/mTOR and Pim 2, associated with cell growth and survival. BLyS blocks the cell volume loss (atrophy) that freshly isolated B cells normally undergo when maintained in vitro while concurrently increasing glycolytic activity and overall metabolism. This atrophy resistance requires Akt/mTOR. We used a genetic approach to resolve the contributions of Akt/mTOR and Pim kinase pathways to BLyS-mediated survival. Pim 2-deficient B cells are readily protected from death by BLyS stimulation, but this protection is completely abrogated by treatment with the mTOR inhibitor rapamycin. Furthermore, rapamycin treatment in vivo
significantly reduces both follicular and marginal zone B cells in Pim-deficient but not healthy hosts. BLyS-dependent survival requires the antiapoptotic protein Mcl-1. Mcl-1 protein levels rise and fall in response to BLyS addition and withdrawal, respectively, and conditional deletion of the Mcl-1 gene renders B cells refractory to BLyS-mediated protection. Because BlyS is required for the normal homeostasis of all B cells, these data suggest a therapeutic strategy simultaneously inhibiting mTOR and Pim 2 could target pathogenic B cells.

L7 ANSWER 2 OF 11 MEDLINE on STN DUPLICATE 2
AN 2008216433 IN-PROCESS
DN PubMed ID: 18374093
TI Rapamycin impairs beta-cell proliferation in vivo.
AU Zahr E; Molano R D; Pileggi A; Ichii H; San Jose S; Bocca N; An W; Gonzalez-Quintana J; Fraker C; Ricordi C; Inverardi L
CS Diabetes Research Institute, University of Miami Miller School of Medicine, Miami, USA.
SO Transplantation proceedings, (2008 Mar) Vol. 40, No. 2, pp. 436-7.
Journal code: 0243532. ISSN: 0041-1345.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS NONMEDLINE; IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 1 Apr 2008
Last Updated on STN: 30 Apr 2008
AB During pregnancy a high rate of beta-cell proliferation occurs, making of this a useful model for the study of islet cell expansion in vivo. We used the murine pregnancy model to assess the effect of Rapamycin treatment on islet cell proliferation in vivo. Rapamycin is routinely used for the prevention of graft rejection in transplanted patients, including islet transplant recipients. As expected, pregnancy led to increased beta-cell proliferation, islet yield and skewing in size distribution after isolation and pancreatic insulin content, when compared to non-pregnant females. Rapamycin treatment resulted in reduced beta

cell proliferation in pregnant mice, while minimal effects of Rapamycin treatment were observed on islet function both in vivo and in vitro. Rapamycin treatment of islets resulted in reduced phosphorylation of p70s6k, a downstream effector molecule of mTOR and increased ERK1/2 phosphorylation. In conclusion, beta-cell replication is reduced under Rapamycin treatment in vivo,
suggesting that this mechanism may be operational and impair beta-cell renewal in transplanted patients.

L7 ANSWER 3 OF 11 MEDLINE on STN DUPLICATE 3
AN 2007151636 MEDLINE
DN PubMed ID: 17230506
TI Mammalian target of rapamycin is activated in human gastric cancer and serves as a target for therapy in an experimental model.
AU Lang Sven A; Gaumann Andreas; Koehl Gudrun E; Seidel Ulrike; Bataille Frauke; Klein Dagmar; Ellis Lee M; Bolder Ulrich; Hofstaedter Ferdinand; Schlitt Hans-Jurgen; Geissler Edward K; Stoeltzing Oliver
CS Department of Surgery, University of Regensburg, Medical Center, Regensburg, Germany.
SO International journal of cancer. Journal international du cancer, (2007 Apr 15) Vol. 120, No. 8, pp. 1803-10.
Journal code: 0042124. ISSN: 0020-7136.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS Priority Journals
EM 200704
ED Entered STN: 14 Mar 2007
Last Updated on STN: 18 Apr 2007
Entered Medline: 17 Apr 2007
AB The mammalian target of rapamycin (mTOR) has become an interesting target for cancer therapy through its influence on oncogenic signals, which involve phosphatidylinositol-3-kinase and hypoxia-inducible factor-1alpha (HIF-1alpha). Since mTOR is an upstream regulator of HIF-1alpha, a key mediator of gastric cancer growth and angiogenesis, we investigated mTOR activation in human gastric adenocarcinoma specimens and determined whether rapamycin could inhibit gastric cancer growth in mice. Expression of phospho-mTOR was assessed by immunohistochemical analyses of human tissues. For in vitro studies, human gastric cancer cell lines were used to determine S6K1, 4E-BP-1 and HIF-1alpha activation and cancer cell motility upon rapamycin treatment. Effects of rapamycin on tumor growth and angiogenesis in vivo were assessed in both a subcutaneous tumor model and in an experimental model with orthotopically grown tumors. Mice received either rapamycin (0.5 mg/kg/day or 1.5 mg/kg/day) or diluent per intra-peritoneal injections. In addition, antiangiogenic effects were monitored in vivo using a dorsal-skin-fold chamber model. Immunohistochemical analyses showed strong expression of phospho-mTOR in 60% of intestinal- and 64% of diffuse-type human gastric adenocarcinomas. In vitro, rapamycin-treatment effectively blocked S6K1, 4E-BP-1 and HIF-1alpha activation, and significantly impaired tumor cell migration. In vivo, rapamycin-treatment led to
significant inhibition of subcutaneous tumor growth, decreased CD31-positive vessel area and reduced tumor cell proliferation. Similar significant results were obtained in an orthotopic model of gastric cancer. In the dorsal-skin-fold chamber model, rapamycin-treatment significantly inhibited tumor vascularization in vivo. In conclusion, mTOR is frequently activated in human gastric cancer and represents a promising new molecular target for therapy.

L7 ANSWER 4 OF 11 MEDLINE on STN DUPLICATE 4
AN 2007572196 MEDLINE
DN PubMed ID: 17671379
TI Rapamycin prevents early steps of the development of diabetic nephropathy in rats.
AU Yang Yi; Wang Jingjing; Qin Ling; Shou Zhangfei; Zhao Jie; Wang Huiping; Chen Ying; Chen Jianghua
CS Kidney Disease Center, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China.
SO American journal of nephrology, (2007) Vol. 27, No. 5, pp. 495-502.
Electronic Publication: 2007-07-20.
Journal code: 8109361. E-ISSN: 1421-9670.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200710
ED Entered STN: 27 Sep 2007
Last Updated on STN: 17 Oct 2007
Entered Medline: 16 Oct 2007
AB BACKGROUND/AIMS: Recent studies suggested the involvement of the Akt/mammalian target of rapamycin (mTOR) pathway in the pathogenesis of diabetic nephropathy. The effect of mTOR blockade by rapamycin in diabetic nephropathy was investigated, but in vivo study of rapamycin treatment in the course of early diabetes is still insufficient. This study was designed to determine the therapeutic effects of rapamycin on diabetic nephropathy at an early stage. METHODS: Diabetes was induced in Sprague-Dawley rats with streptozotocin, and rapamycin (1 mg/kg) was administered by daily gavage for 4 weeks. Renal structural changes and some factors involved in the early pathogenesis of diabetic nephropathy were tested. The activation level of the Akt/mTOR pathway was also determined. RESULTS: Rapamycin treatment reduced albuminuria, glomerular enlargement, glomerular basement membrane thickening, renal macrophage recruitment, and levels of renal mRNA expression of proliferating cell nuclear antigen, transforming growth factor-beta1, vascular endothelial growth factor, and monocyte chemoattractant protein-1 without change in blood glucose level and blood pressure in experimental diabetic rats. In addition, treatment with rapamycin also down-regulated the enhanced levels of renal p-Akt, phospho-p70S6 kinase, and phospho-ribosomal S6 protein in diabetic rats. CONCLUSIONS: Rapamycin treatment can prevent the early renal structural changes of diabetes in experimental rats, and thus halt the early steps of the development of diabetic nephropathy. mTOR blockade might be beneficial for the treatment of diabetic nephropathy.

L7 ANSWER 5 OF 11 MEDLINE on STN
AN 2007415707 MEDLINE
DN PubMed ID: 17390104
TI Specific mTOR inhibitor rapamycin enhances cytotoxicity induced by alkylating agent 1-(4-amino-2-methyl-5-pyrimidinyl)methyl-3-(2-chloroethyl)-3-nitrosourea (ACNU) in human U251 malignant glioma cells.
AU Tanaka Kazuhiro; Sasayama Takashi; Mizukawa Katsu; Kawamura Atsufumi; Kondoh Takeshi; Hosoda Kohkichi; Fujiwara Toshiyoshi; Kohmura Eiji
CS Department of Neurosurgery, Kobe University Graduate School of Medicine, 7-5-1, Kusunoki-cho, Chou-ku, Kobe, 650-0017, Japan.. hiro2804@med.kobe-u.ac.jp
SO Journal of neuro-oncology, (2007 Sep) Vol. 84, No. 3, pp. 233-44.
Electronic Publication: 2007-03-28.
Journal code: 8309335. ISSN: 0167-594X.
CY Netherlands

DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS Priority Journals
EM 200710
ED Entered STN: 20 Jul 2007
Last Updated on STN: 24 Oct 2007
Entered Medline: 23 Oct 2007
AB Loss of the PTEN tumor suppressor gene and amplification of the epidermal growth factor receptor (EGFR), which is common in malignant gliomas, result in activation of the mammalian target of rapamycin (mTOR). Rapamycin is a highly specific inhibitor of mTOR and induces a cytostatic effect in various glioma cell lines. DNA-damaging agents such as nitrosourea are widely used in malignant glioma treatment; therefore, we investigated the effect of rapamycin on cell growth and death in combination with 1-(4-amino-2-methyl-5-pyrimidinyl)methyl-3-(2-chloroethyl)-3-nitrosourea (ACNU, nimustine hydrochloride) in human glioma cells. In U251 malignant glioma (U251MG) cells, we confirmed that rapamycin enhanced ACNU-induced apoptosis. We found that rapamysin inhibited ACNU-induced p21 induction, and knocking down of p21 protein by siRNA enhanced ACNU-induced apoptosis in U251MG cells. Furthermore, adenovirus-mediated over-expression of p21 protein rescued U251MG cells from apoptosis induced by ACNU and rapamycin. Finally, treatment of intracerebral U251MG xenografts with a combination of rapamycin and ACNU in vivo resulted in statistically prolonged median survival ($P<0.05$). These results suggest that rapamycin in combination with DNA-damaging agents may be efficacious in the treatment of malignant gliomas.

L7 ANSWER 6 OF 11 MEDLINE on STN DUPLICATE 5
AN 2003268127 MEDLINE
DN PubMed ID: 12668683
TI Regulation of the phosphatidylinositol 3-kinase, Akt/protein kinase B, FRAP/mammalian target of rapamycin, and ribosomal S6 kinase 1 signaling pathways by thyroid-stimulating hormone (TSH) and stimulating type TSH receptor antibodies in the thyroid gland.
AU Suh Jae Mi; Song Jung Hun; Kim Dong Wook; Kim Ho; Chung Hyo Kyun; Hwang Jung Hwan; Kim Jin Man; Hwang Eun Suk; Chung Jongkyeong; Han Jeung-Hwan; Cho Bo Youn; Ro Heung Kyu; Shong Minho
CS Laboratory of Endocrine Cell Biology, Department of Internal Medicine, Chungnam National University School of Medicine, 640 Daesadong Chungku, Taejon 301-040, Korea.
SO The Journal of biological chemistry, (2003 Jun 13) Vol. 278, No. 24, pp. 21960-71. Electronic Publication: 2003-03-30.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200307
ED Entered STN: 10 Jun 2003
Last Updated on STN: 23 Jul 2003
Entered Medline: 22 Jul 2003
AB Thyroid-stimulating hormone (TSH) regulates the growth and differentiation of thyrocytes by activating the TSH receptor (TSHR). This study investigated the roles of the phosphatidylinositol 3-kinase (PI3K), PDK1, FRAP/mammalian target of rapamycin, and ribosomal S6 kinase 1 (S6K1) signaling mechanism by which TSH and the stimulating type TSHR antibodies regulate thyrocyte proliferation and the follicle activities in vitro and in vivo. The TSHR immunoprecipitates exhibited PI3K activity, which was higher in the cells treated with either TSH or 8-bromo-cAMP. TSH and cAMP

increased the tyrosine phosphorylation of TSHR and the association between TSHR and the p85alpha regulatory subunit of PI3K. TSH induced a redistribution of PDK1 from the cytoplasm to the plasma membrane in the cells in a PI3K- and protein kinase A-dependent manner. TSH induced the PDK1-dependent phosphorylation of S6K1 but did not induce Akt/protein kinase B phosphorylation. The TSH-induced S6K1 phosphorylation was inhibited by a dominant negative p85alpha regulatory subunit or by the PI3K inhibitors wortmannin and LY294002. Rapamycin inhibited the phosphorylation of S6K1 in the cells treated with either TSH or 8-bromo-cAMP. The stimulating type TSHR antibodies from patients with Graves disease also induced S6K1 activation, whereas the blocking type TSHR antibodies from patients with primary myxedema inhibited TSH- but not the insulin-induced phosphorylation of S6K1. In addition, rapamycin treatment in vivo inhibited the TSH-stimulated thyroid follicle hyperplasia and follicle activity. These findings suggest an interaction between TSHR and PI3K, which is stimulated by TSH and cAMP and might involve the downstream S6K1 but not Akt/protein kinase B. This pathway may play a role in the TSH/stimulating type TSH receptor antibody-mediated thyrocyte proliferation in vitro and in the response to TSH in vivo.

L7 ANSWER 7 OF 11 MEDLINE on STN DUPLICATE 6
AN 1998187625 MEDLINE
DN PubMed ID: 9528776
TI A heat-sensitive Arabidopsis thaliana kinase substitutes for human p70s6k function in vivo.
AU Turck F; Kozma S C; Thomas G; Nagy F
CS Friedrich Miescher-Institute, Basel, Switzerland.
SO Molecular and cellular biology, (1998 Apr) Vol. 18, No. 4, pp. 2038-44. Journal code: 8109087. ISSN: 0270-7306.
CY United States
DT Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS Priority Journals
OS GENBANK-Y14052
EM 199805
ED Entered STN: 29 May 1998
Last Updated on STN: 3 Mar 2000
Entered Medline: 21 May 1998
AB In mammalian cells, mitogen-induced phosphorylation of ribosomal protein S6 by p70s6k has been implicated in the selective translational upregulation of 5'TOP mRNAs. We demonstrate here that the homologous Arabidopsis thaliana protein, AtS6k2, ectopically expressed in human 293 cells or isolated from plant cells, phosphorylates specifically mammalian and plant S6 at 25 degrees C but not at 37 degrees C. When Arabidopsis suspension culture cells are shifted from 25 to 37 degrees C, the kinase becomes rapidly inactivated, consistent with the observation that heat shock abrogates S6 phosphorylation in plants. Treatment with potato acid phosphatase reduced the specific activity of immunoprecipitated AtS6k2 threefold, an effect which was blocked in the presence of 4-nitrophenyl phosphate. In quiescent mammalian cells, AtS6k2 is activated by serum stimulation, a response which is abolished by the fungal metabolite wortmannin but is resistant to rapamycin. Treatment of mammalian cells with rapamycin abolishes in vivo S6 phosphorylation by p70s6k; however, ectopic expression of AtS6k2 rescues the rapamycin block. Collectively, the data demonstrate that AtS6k2 is the functional plant homolog of mammalian p70s6k and identify a new signalling pathway in plants.

L7 ANSWER 8 OF 11 MEDLINE on STN DUPLICATE 7

AN 97032620 MEDLINE
DN PubMed ID: 8878395
TI Effect of in vivo rapamycin treatment on de novo T-cell development in relation to induction of autoimmune-like immunopathology in the rat.
AU Damoiseaux J G; Beijleveld L J; Schuurman H J; van Breda Vriesman P J
CS Department of Immunology, Rijksuniversiteit Limburg, Maastricht, The Netherlands.
SO Transplantation, (1996 Oct 15) Vol. 62, No. 7, pp. 994-1001. Journal code: 0132144. ISSN: 0041-1337.
CY United States
DT Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS Priority Journals; AIDS
EM 199612
ED Entered STN: 28 Jan 1997
Last Updated on STN: 29 Jan 1999
Entered Medline: 2 Dec 1996
AB Cyclosporine (CsA) and FK506 are structurally unrelated immunosuppressants, but function in similar ways. FK506 and rapamycin (RAPA), on the other hand, have structural similarities, but act by different mechanisms to yield immunosuppression. Besides their immunosuppressive action, CsA and FK506 are known to interfere with T-cell development. CsA treatment after lethal X-irradiation and syngeneic bone marrow transplantation results in autoimmune disease, which is referred to as CsA-induced autoimmunity. In this study, we examined the effect of RAPA on T-cell development by flow cytometry and immunohistochemistry in female Lewis and Brown Norway rats. Irradiation and syngeneic bone marrow transplantation were performed before a 4-week course of RAPA administration to determine de novo T-cell development in relation to possible autoimmune phenomena. RAPA interfered with the maturation of thymocytes to the CD4+CD8+ DP stage, which resulted in a relative increase in TCRalphabeta(-) immature thymocytes, localized in a rim along the outer cortex. The thymus of RAPA-treated animals had a thinner cortex, leading to stronger thymic atrophy. In the periphery, only a few T cells were observed at the end of RAPA treatment. In the Lewis rat, a normal CD4/CD8 T-cell ratio and an increased Th1/Th2 ratio was observed within the T-cell population. Six weeks after cessation of RAPA therapy, the T-cell compartment was restored to normal, with respect to number and phenotype. In Brown Norway rats, however, T-cell areas were barely detectable at the end of RAPA treatment. The CD4/CD8 T-cell ratio was decreased as a result of a lower number of CD4 T cells; the Th1/Th2 ratio was increased but Th2 remained higher. Similar to Lewis rats, the situation was almost normalized 6 weeks after cessation of RAPA administration. However, Brown Norway rats, in contrast to Lewis rats, showed T-cell infiltration and concomitant induction of MHC class II in the submandibular salivary gland, as well as insulitis, in the pancreas. Possible relationships to Sjogren's disease and diabetes remain to be established.

L7 ANSWER 9 OF 11 MEDLINE on STN DUPLICATE 8
AN 93370918 MEDLINE
DN PubMed ID: 8363274
TI Prevention and treatment of allograft rejection in vivo by rapamycin: molecular and cellular mechanisms of action.
AU Morris R E
CS Department of Cardiothoracic Surgery, Stanford University School of Medicine, California 94305-5247.
SO Annals of the New York Academy of Sciences, (1993 Jun 23) Vol. 685, pp. 68-72.

Journal code: 7506858. ISSN: 0077-8923.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199309
ED Entered STN: 15 Oct 1993
Last Updated on STN: 29 Jan 1999
Entered Medline: 24 Sep 1993

L7 ANSWER 10 OF 11 MEDLINE on STN DUPLICATE 9
AN 92234464 MEDLINE
DN PubMed ID: 1568729
TI Effects of rapamycin on cultured hepatocyte proliferation and gene expression.
AU Francavilla A; Carr B I; Starzl T E; Azzarone A; Carrieri G; Zeng Q H
CS Department of Surgery, University Health Center of Pittsburgh, Pennsylvania 15213.
NC CA 35373 (United States NCI)
DK 29961 (United States NIDDK)
SO Hepatology (Baltimore, Md.), (1992 May) Vol. 15, No. 5, pp. 871-7.
Journal code: 8302946. ISSN: 0270-9139.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LA English
FS Priority Journals
EM 199205
ED Entered STN: 12 Jun 1992
Last Updated on STN: 29 Jan 1999
Entered Medline: 26 May 1992
AB Rapamycin, a potent immunosuppressive drug that disrupts normal signal-transduction processes, inhibited hepatocyte proliferation without evidence of inherent cytotoxicity in rat hepatocytes cultured in conventional medium or in a medium enriched with epidermal growth factor. The antiproliferative effect was dose dependent, uninfluenced by the concentration of epidermal growth factor in the medium and long lasting after a brief exposure. The effect of rapamycin was unaltered by the concomitant presence of FK 506 in the medium, suggesting that different binding affinities of these two drugs or even a separate rapamycin binding site may exist. Hepatocytes harvested 12 and 24 hr after partial hepatectomy were progressively less responsive to the antiproliferative effect of rapamycin. The gene expression of transforming growth factor-beta was reduced under in vivo rapamycin treatment, but at the same time the gene expression of albumin and glyceraldehyde-3-phosphate dehydrogenase was unchanged or increased. The experiments confirm that rapamycin has inherent growth-control qualities, and they strengthen the hypothesis that the recently defined immunophilin network is central to many aspects of cellular growth control.

L7 ANSWER 11 OF 11 MEDLINE on STN DUPLICATE 10
AN 93138709 MEDLINE
DN PubMed ID: 1487312
TI Brief treatment with rapamycin in vivo increases responsiveness to alloantigens measured by the mixed lymphocyte response.
AU Mohacsi P J; Morris R E
CS Department of Cardiothoracic Surgery, Stanford University School of Medicine, CA 94305-5247.

SO Immunology letters, (1992 Dec) Vol. 34, No. 3, pp. 273-8.
Journal code: 7910006. ISSN: 0165-2478.
CY Netherlands
DT (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS Priority Journals
EM 199302
ED Entered STN: 12 Mar 1993
Last Updated on STN: 29 Jan 1999
Entered Medline: 25 Feb 1993
AB Rapamycin (RPM) is a macrolide fermentation product that prolongs rodent allograft survival more potently and effectively than cyclosporin A (CsA) and FK506. Experiments in vitro have shown that RPM inhibits lymphoproliferation by mechanisms of action that are different from other immunosuppressants. Much less is known, however, about the effects of RPM on immune cells in vivo compared to other immunosuppressive drugs. Others have shown that in vivo treatment with CsA suppresses the responsiveness of cells in the mixed lymphocyte response (MLR). Therefore, to investigate the effects of RPM in vivo, rats were treated with RPM and their lymphoid cells used as responder cells in the MLR. We confirmed that the proliferation of cells in the MLR was decreased after treatment with CsA in vivo. In contrast, treatment with RPM in vivo greatly increased the proliferative response to alloantigen in the MLR. These findings show that the effects of RPM and CsA on immune cells in vivo differ. Perhaps the cells proliferating in the MLR after in vivo RPM treatment play a role in the regulation of the immune system that enables this immunosuppressant to prolong allograft survival so effectively in rodents.